Lesch-Nyhan Disease and Related Disorders of Purine Metabolism

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Abstract
Lesch-Nyhan disease is the most severe or complete phenotype of deficiency in hypoxanthine-guanine phosphoribosyltransferase (HPRT). Other variant enzymes are found in patients without abnormality in behavior or mental development; and there are intermediate phenotypes in which enzyme activity is intermediate. A considerable number and variety of mutations in the HPRT gene have been discovered. (Tzu Chi Med J 2007; 19(3):105–108)

1. Introduction
The most common of the diseases of purine metabolism and of the hyperuricemias of childhood is deficiency of hypoxanthine-guanine phosphoribosyltransferase (HPRT), and among patients with HPRT deficiency, the majority have the classic Lesch-Nyhan disease (1,2). This X-linked recessive disorder of purine metabolism results from deficiency of the activity of the enzyme HPRT (Fig. 1) (3). HPRT deficiency leads to a variety of clinical phenotypes ranging in severity from the classic Lesch-Nyhan disease in which neurologic and behavioral features are seen, along with clinical manifestations of hyperuricemia that are shared with patients with gout to patients with normal neurology and behavior who have only manifestations directly attributable to uric acid, whom we have referred to as variants or partial variants. An intermediate group we have termed neurologic variants have a variety of

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neurologic manifestations without the characteristic self-injurious behavior of the Lesch-Nyhan variant.

2. Clinical presentation

In the classic Lesch-Nyhan phenotype, affected infants develop normally for the first 4–6 months. The first sign of the disease is usually the appearance of what looks like orange sand in the diapers. Delayed neurologic development becomes apparent within the first year; the child does not sit alone or loses this ability. Patients with this phenotype never learn to stand unassisted or to walk. Ultimately, if securely fastened around the chest or waist, the child can sit in a chair or wheelchair. During the first year, extrapyramidal signs develop. Involuntary movements may be choreic or athetoid as well as dystonic. Severe action dystonia is the major motor feature.

Episodic opisthotonus or opisthotonic spasm regularly present in our experience, reported in 25% (4), may lead to cervical spinal cord injury.

Signs of pyramidal tract involvement develop during the first years of life, and the accompanying spasticity is severe, often leading to dislocation of the hips. Patients have hyperreflexia and ankle clonus; a positive Babinski’s response is present in most. Scissoring the legs is common. Dysarthria and dysphagia are other features of the disease, and the dysarthria can combine with the motor defect and behavior to make proper assessment of mental capabilities difficult. Most patients eat poorly, and most of them vomit. Mental development may be retarded; the IQ, as measured, is usually in the range of 40–70. However, the behavior and motor defect make testing difficult. Some patients have had normal cognitive function, and a few have been successful mainstream students.

Aggressive, self-mutilative behavior is the single most distinctive feature of Lesch-Nyhan disease and in our experience has always been present in patients with the fully developed syndrome. Patients bite their lips, tongue and fingers, leading to loss of tissue and partial amputations. Patients are not insensitive to pain, and they scream in pain when they bite and are usually relieved when restrained to prevent self-injury. Physical restraints and extraction of teeth are the only effective methods of preventing the behavior. Aggressive behavior is also directed to others; patients bite, hit and kick. Detailed behavioral analysis of 22 patients revealed characteristic behavior/profiles of aggression, distractibility, anxiety and social problems (5).

Patients with HPRT deficiency are all hyperuricemic, and uric acid levels are between 5 and 10 mg/dL, while 3–4 mg of uric acid per mg creatinine (1.9±0.9 mmol/mol creatinine) are found in the urine. Normal children excrete less than 1 mg of uric acid/mg creatinine (0.2 mmol/mol creatinine). Patients may have normal serum levels if they are efficient excretors and may appear normal if adult male standards are used. Urinary data for uric acid can be spuriously low as a result of bacterial contamination. Accordingly, spot samples promptly frozen are better than 24-hour collections.

As a result of the accumulation of uric acid, patients manifest gout, arthritis, tophi, painful crystalluria, hematuria, nephrolithiasis, urinary tract infection and, in untreated patients, end-stage urate nephropathy.

Patients have also had megaloblastic anemia, severe enough in some to require blood transfusions. Macrocytosis or megaloblastic changes in the marrow have also been found in the absence of clinical anemia.

A preliminary diagnosis of classic Lesch-Nyhan syndrome can be made based on the phenotype. A serum concentration in a child of more than 4–5 mg uric acid/dL and a urine uric acid to creatinine ratio of 3–4 are supportive. Definitive diagnosis requires analysis of the HPRT activity of the HPRT enzyme. This is most conveniently assayed in erythrocytes. Dried blood spots on filter paper, as in newborn screening programs, provide for a stable source of enzyme for analysis of samples sent from distances.

3. The HPRT enzyme

HPRT (EC 2.4.2.8) catalyzes the reaction of hypoxanthine and guanine with 5-phosphoribosyl-1-pyrophosphate (PRPP) to form the nucleotides inosinic acid (IMP) and guanylic acid (GMP) (Fig. 1). HPRT is actively expressed in the cytoplasm of every cell of the body; highest levels are found in the basal ganglia. In HPRT deficiency, the underutilization of hypoxanthine and guanine leads to increased excretion of the degradation product uric acid, and the accompanying underutilization of PRPP gives rise to increased activity in the de novo pathway, increasing uric acid production.

In Lesch-Nyhan disease, the activity of HPRT in erythrocytes approximates zero (3,6). Patients who do not have the full clinical phenotype of the classic Lesch-Nyhan patient have activity that is low but not absent. Among the three groups, the classic Lesch-Nyhan disease, the neurologic variants, and those with hyperuricemia, no consistent correlation between enzyme activity as measured in the red cell lysate and clinical phenotype has emerged. However, when enzyme activity is measured in intact cultured fibroblasts, there is a rough inverse correlation between HPRT activity and the severity of clinical manifestations (6).

In partial variants with neurologic disease, hyperuricemia is present together with the typical extrapyramidal and pyramidal symptoms found in the classic Lesch-Nyhan patient. Intelligence is normal or near normal, and behavior may appear normal. The
neurologic examination of these patients is indistinguishable from that of the patient with classic Lesch-Nyhan disease.

A distinct clinical phenotype with partial HPRT deficiency (7.5% of normal enzyme activity) has been reported in a family with four affected members (7). Each member displayed a phenotype of atypical neurologic disease characterized by spasticity, increased deep tendon reflexes, and a positive Babinski’s response, but no dystonia or choreoathetosis; mental retardation was mild.

4. Molecular genetics

The gene for HPRT is coded on the X chromosome and mapped to the distal part of the long arm at position Xq2.6-Xq2.7. The disease is transmitted in an X-linked recessive fashion. It is almost exclusively a disease of the male, but seven affected females have been observed (8,9).

HPRT consist of 44 kb of DNA spread over 9 exons (Fig. 2). The gene is copied into the mRNA which is 1.6 kb in length but the actual reading frame, the piece that codes for the protein, is smaller. It contains 217 amino acids in a subunit which then functions in a tetramer.

The 302 known mutations represent a wide variety. In general, each family has been found to have its own unique mutation in the HPRT gene (10,11). Every possible type of mutation has been described within this gene: point mutations or single base substitutions leading to amino acid substitution; nonsense point mutations which lead to stop codons and truncated proteins; point mutations at splice sites, nucleotide sequences that are designed to remove introns in the formation of mature mRNA, leading to a number of problems with the mRNA. For instance, one splice site mutation in a Lesch-Nyhan patient destroys the normal splicing site and reading goes from exon 1 to exon 3, skipping exon 2. Another deletes exon 7. Splicing sites have consensus sequences that are conserved among the various splicing sites, and within the gene there are some sequences that are cryptic splicing sites which look like splicing sites. Some may be almost perfect sequences to lead to splicing site, but many do not function well. In some situations in the HPRT gene, the normal splice site is mutated and does not work, but a cryptic splice which is less functional nevertheless functions to some extent. In one instance, the cryptic splicing sites between exons 5 and 6 function so that exon sequences are not lost but a bit of the sequence of the intron is retained. Cryptic splicing within the exon also leads to removal of a piece of exon 9.

A number of deletions have been documented in the HPRT gene of Lesch-Nyhan patients. Deletions have been described for exon 4, exons 3, 6, and 7, while larger pieces of the gene have also been found, for instance deletion of exons 4 to 9 or even the whole gene. Genotype–phenotype correlations are emerging in this expanding database. In general, major disruptions such as deletions, large insertions, splice mutation, nonsense mutations or amino acid substitutions that are not conservative are associated with the classical Lesch-Nyhan phenotype.

Among point mutations found in variants in whom there is some residual activity, there is often a conservative amino acid substitution. At any given position in the gene, conservative change leads to variant, and a non-conservative change leads to the classical Lesch-Nyhan phenotype. For instance, in exon 2, there is normally a glycine at position 16. If it is changed to serine (a conservative change), the phenotype is variant. If it is changed to aspartic acid (a non-conservative change), the patient has the classic Lesch-Nyhan phenotype. In another example at position 194, when the acidic amino acid aspartic is changed to glutamic (a conservative transition), the phenotype is a variant, while a change to tyrosine or histidine (a very non-conservative change) would lead to a Lesch-Nyhan phenotype. The nature of the mutation remains only a rough guide for predicting phenotype.

In general, phenotype correlates better with the amount of residual enzyme activity displayed in whole cell assays (6). The classic Lesch-Nyhan disease is found when enzyme activity approximates zero, or close to it, and the partial phenotype occurs when an appreciable amount of enzyme activity can be demonstrated. A few exceptions have been reported in which classic phenotypes have accompanied relatively sizable activities (12,13) or mild variant phenotype with no demonstrable enzyme activities (12–14). Explanations for the exceptions include discrepancies between the activity of an aberrant enzyme structure.
when removed from its *in vivo* cellular environment, as has been demonstrated in difference between activity of an enzyme in lysates versus whole cell preparations. Also, mutations which change the kinetics of an enzyme may be measured at very different concentrations, usually greater, than one finds *in vivo*. Some mutations are unstable; for instance, two duplications were reported to recombine, restoring normal enzyme activity in some cells, creating a mosaic of normal and abnormal cells (12–14).

A considerable amount of information has been obtained from analysis of the nature of mutation. In a family in which the mutation is known, this is the method of choice for the detection of heterozygotes and for prenatal diagnosis. It can be of use in predicting phenotype especially in a young presymptomatic infant born into a family with no precedent patients. Enzyme analysis via the intact well method remains the most reliable method for this purpose. As the issue of prognosis is so important, it is prudent in such an instance to utilize both methods.

**References**